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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/098,626	FARWICK ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1,2,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/7/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on February 17, 2004), Applicants filed an election received on March 8, 2004. Claims 1-19 are pending in the instant Office action.

Election

2. Applicant's election of Group III in a paper received on March 3, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

Upon consideration of art for the elected Group, the Examiner has decided to withdraw the restriction between Groups III and IV, methods using attenuated 1-phosphofructokinase and methods using attenuated 6-phosphofructokinase. Thus, Claims 3-17 will be examined in their entirety. Claims 1-2 and 18-19 are withdrawn from consideration as non-elected inventions.

Priority

3. The instant application is granted the benefit of priority for the foreign application 10112992.0 filed in Germany on March 17, 2001 as requested in the declaration.

Receipt is acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file. Said papers are not in English and, thus, cannot be used to assess the earliest effective filing date of the claimed subject matter.

Information Disclosure Statement

4. The information disclosure statement filed on August 7, 2002 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy. The Examiner has corrected the placement of a reference, now found in "Foreign Patent Documents". The international search report has been considered and is crossed out since it is not printed on the face of the patent.

Sequence Compliance

5. The sequence listing filed on May 20, 2004 in computer readable form and paper copy brings the instant application into compliance with the sequence rules.

Objections to the Specification

6. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Process for the Preparation of Amino Acids by Using Coryneform Bacteria with Attenuated 6-Phosphofructokinase or 1-Phosphofructokinase Activity---

7. The specification is objected to for being confusing in a reference to "EP: 00110021.3" in paragraph [0028]. The identity of the foreign reference is unclear. Clarification is required.

Claim Objections

8. Claim 11 is objected to for having an improper format; all claims must end with a period. Correction is required.

9. Claim 4 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The added limitation of "enriching" does not further limit the scope of the independent claim. The specification does not teach any means of "enriching" other than the limitations of Claim 3. Thus, it would seem that simply fermenting will enrich with amino acids and Claim 4 does not further limit the scope of Claim 3.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 9-10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear from the language of Claim 9 if the achieving mentioned is a real claim limitation or not. The last three lines of the claim seem to describe the attenuated sequence in the bacteria but not necessarily as an additional method step.

Moreover, the overall concept of Claims 9 and 10 is confusing as to the use of 300 to 800 base pairs extensions of the pfk genes for attenuation. For example, the sequence listing describes SEQ ID NO:1 as "pfkA-Gen" indicating that the sequence is not full-length pfkA due to an insertion of Gen; this is not the case for SEQ ID NO:1, which exactly encodes 343 amino acid 6-phosphofructokinase. If SEQ ID NO:1 encodes pfkA-Gen, the extensions would clearly assist in recombination wherein SEQ ID NO:1 would homologously recombine with endogenous

pfkA and introduce a non-functional pfkA-Gen. However, this is not the case, and homologous recombination of SEQ ID NO:1 with endogenous pfkA would result in no change in pfkA expression (i.e., no attenuation). Clarification is required.

11. Claim 10 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The positions of the elongation are inconsistent with the sequence listing rendering Claim 10 confusing. SEQ ID NO:3 has 1-608 N-terminal elongation and 1599-2160 C-terminal elongation; SEQ ID NO:1 has 1-631 N-terminal elongation and 1661-2234 C-terminal elongation. Clarification is required.

12. Claim 10 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The wherein clause is improper English and must be corrected for clarity of the claim.

13. Claims 11 and 12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of "genes in the biosynthesis pathway" and the "metabolic pathways that reduce the formation of the L-amino acid" are unclear. Metabolic pathways in coryneform are complex and overlapping with far-reaching effects that might produce or reduce amino acid formation. A clear definition of which enzymes are involved is required, either from the specification or the art, for all the L-amino acids.

14. Claims 15-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear exactly which genes must be enhanced or attenuated in the instant claims. Take the phrase "the pyc gene coding for pyruvate carboxylase", for example. If *C. glutamicum* is the microorganism, must the *C. glutamicum* pyc gene be used in the methods to enhance the pyc gene or can *any* pyruvate carboxylase gene (from any organism) enhance the pyc gene in the method? Additionally, if a pyruvate carboxylase gene was named ---gene A--- (and not pyc), would its use read on the instant claims? Clarification is required.

15. Claim 15 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The line having "simultaneously" is unclear in which instance lysE must be also enhanced. Clarification is required.

16. Claims 15-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The words "coding for lysine export" are used improperly because lysE encode a protein that exports lysine; the gene itself does not perform this function. Also, the nature of a zwa1 and zwa2 protein is unclear. While indication of C. glutamicum genes is noted in the specification, the claims are not limited to this. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 15-16 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 15 and 16 are drawn to methods using microorganisms with affected genes wherein the gene that is claimed solely by name and without any structural limitations; the specific genes are as follows: (1) coding for lysine export, (2) zwa1 protein, and (3) zwa2 protein.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical

characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

Unlike genes such as pyc encoding pyruvate carboxylase, the instant genes encode enzymes that do not have well known structures associated with them in the art. The instant specification describes one or two examples of each on page 12-13. In the claims, these genes are only described according to the functional characteristics (or name) of the enzymes they encode; no structural relationship is described or used. Thus, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure. Therefore, claims drawn to methods using microorganisms affecting in these genes are also not adequately described.

18. Claims 3-17 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for attenuating genes by their deletion, does not reasonably provide enablement for attenuating genes by substituting with attenuated alleles. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To produce the products necessary to practice the claimed methods would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404).

Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

On page 4, the specification describes attenuation as including using weak promoters or alleles encoding enzymes with lower activity; and in the Examples, an endogenous pfkB gene is deleted from *C. glutamicum* using pXK99EmobpfkB. Deletion of pfkA and/or pfkB in *C. glutamicum* is enabled. However, sufficiently weakening unknown promoters and/or identifying alleles encoding phosphofructokinases with lower activities would require undue experimentation. The specification provides no examples or guidance as to the construction of such attenuated pfk genes. The nature of the invention is such that while *C. glutamicum* pfk is well known, alteration to reduce activity, particularly in allelic variant form, are not well known. One of skill in the art would be unable to predict the structure of such variants and, thus, would be unable to practice the claimed methods to the full extent of their scope. In particular, the Examiner notes that WO 00/77172 (see IDS) teaches an increase in lysine production of about 10% when 6-phosphofructokinase is enhanced in *C. glutamicum*; this is in direct contrast to the

about 10% increase of lysine when 6-phosphofructokinase is deleted in *C. glutamicum* in the instant application. Thus, attenuation, particularly for the purpose of amino acid production, is wholly unpredictable.

The Examiner notes that this rejection applies to both attenuation of the pfk genes as well as attenuation of additional genes (Claims 12 for partially switched off and 16).

19. Claim 15 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for enhancing genes by their overexpression, does not reasonably provide enablement for enhancing genes by other means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To produce the products necessary to practice the claimed methods would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

On page 11, the specification describes enhancement as including using strong promoters or genes encoding enzymes with higher activity. Overexpression of genes to enhance them in any coryneform is enabled since art-described means of overexpressing genes are well know. However, sufficiently strengthening unknown promoters and/or identifying alleles encoding enzymes with higher activities would require undue experimentation. The specification provides no examples or guidance as to the construction of such enhanced genes. The nature of the invention is such that while enzymes, such as aspartate kinase, are well known, alteration to increase activity, particularly in allelic variant form, are not well known. One of skill in the art

would be unable to predict the structure of such variants and, thus, would be unable to practice the claimed methods to the full extent of their scope.

20. Claim 14 is rejected under 35 U.S.C. § 112, first paragraph, enablement, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. To produce the products necessary to practice the claimed methods would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

No guidance or working examples of reduction of phosphofructokinase catalytic properties are described. The nature of the invention is such that the encoded protein catalyzes specific reactions; affecting such an interaction requires unpredictable experimentation. The art is without examples of such proteins. Thus, the claim is not enabled.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

21. Claims 3, 4, 8-10, 13 and 17 are rejected under 35 U.S.C. § 102(e) as being anticipated by Hanke *et al.* (USPN 6,465,238). The instant claims are drawn to methods of making lysine using *C. glutamicum* with reduced 6-phosphofructokinase expression. Claims 9-10 are included because the limitations of using elongated sequence are unclear as noted above.

Hanke *et al.* teach disrupting endogenous pfkA in *C. glutamicum* (see Example 3) wherein expression of 6-phosphofructokinase is abolished; Hanke *et al.* also teach methods of producing L-amino acids, such as lysine, using the bacterial cells taught (see column 1, lines 56-61, and column 2, line 57) and the mutant made in Example 3 inherently produces lysine.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 5-7, 11, 12, 15, 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanke *et al.* (USPN 6,465,238). The instant claims are drawn to methods of making and isolating lysine, with fermentation and/or biomass constituents present, using *C. glutamicum* with reduced 6-phosphofructokinase expression as well as enhanced and attenuated other genes. Claims 11 and 12 are included due to the vagueness of the term "pathways" as noted above.

Hanke *et al.* teach as described above. Hanke *et al.* also teach isolating lysine by means known in the art, which means include retaining fermentation and/or biomass constituents (see column 18, Table A). Hanke *et al.* also teach further altering the *C. glutamicum* for better amino

acid production by means of enhancing glucose 6-phosphate dehydrogenase (see column 5, lines 1-10) and by means of decreasing 6-phosphoglucose isomerase (see column 5, lines 25-39), also known as glucose-6-phosphate isomerase in instant Claim 16. Hanke *et al.* do not teach all the above alterations specifically with the *C. glutamicum* pfkA mutant taught.

At the time of the invention, it would have been obvious to combine all the iterations of Hanke *et al.* into one *C. glutamicum* host cell for the production and isolation of lysine due to the specification disclosure in Hanke *et al.* and the preferred embodiments. One would have been motivated to practice such a method due to the commercial demand for lysine and means of its production (see Hanke *et al.*, column 1, lines 17-30). One would have had a reasonable expectation of success due to the high skill in the art for such genetic manipulations in *C. glutamicum* as well as *C. glutamicum's* natural ability to produce lysine, which ability is unlikely to be significantly altered so as to no longer produce lysine by such genetic alterations.

Other Art of Record

23. The following are cited to complete the record:

a) Hermann (DE 10135051A1) teaches producing amino acids in Enterobacteriaceae with attenuated pfkB (see Abstract); this reference is not available as prior art.
b) No prior art relating to methods of making amino acids using *C. glutamicum* with a deleted pfkB gene (1-phosphofructokinase) is noted.

Conclusion

24. Claims 3-17 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Examiner
Art Unit 1652

May 13, 2004